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THE FUNCTIONAL REACTIONS OF THE HUMAN THYROID *

A CONTRIBUTION TO ITS HISTOPHYSIOLOGY

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Many attempts have been made to get a better understanding of the histophysiology of the thyroid gland. If Graves' disease is nothing more than a severe condition of hyperthyroidism the structure of the enlarged gland should give us the key to the problem. Unfortunately the arguments in favor of a condition of dysthyroidism cannot be discarded altogether. On the other hand, the histology of toxic goiters (exophthalmic and non-exophthalmic) is by no means a constant one and the efforts made thus far to explain the severity of the clinical course by the histological features have not met with uniform success. The statistics of Wilson [1] published in 1914 show that the clinician and the pathologist are in agreement in only 75 per cent of the cases examined.

The use of the tinctorial reactions of the colloid, suggested by Kraus [2] and Troell,[3] has not improved this percentage by any great degree. However, the concept of the "Wucherungspolstern" introduced by Sanderson-Damberg [4] has enabled Hellwig [5] to get more satisfactory results. This tends to prove that a better knowledge of the finer histological structures will clear up many questions of interest in the toxic goiter problem. Unfortunately, researches along these lines are now hampered with new difficulties which arise from the prevailing Plummer preoperative treatment with iodine (Mayer and Fürstenheim [6]). The accumulation of colloid is a disturbing factor in the interpretation of the morphological findings.

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Another method of approach would consist in looking for distinctive morphological peculiarities of endemic goiters with or without hyperthyroidism. Here again a uniform morphological standard is lacking. Nothing enables us to say whether an enlarged gland does or does not elaborate more thyroxin. As Wegelin [7] points out, our shortcomings may be due to several causes, among which our imperfect knowledge of the histophysiology of the thyroid is a prominent one.

Progress in this direction is needed and the conditions are too intricate to make headway by the study of goiter material. In our opinion progress will be attained only by a scheme of investigation wherein the cellular reactions are closely correlated with a definite functional phase of development, such as metamorphosis (Uhlenhuth [8]), or with a stimulation of the gland measured by the increase of the basal metabolism. The recent work of Okkels, Krogh and Lindberg,[9] who make use of the thyrotropic hormone as a stimulant, opens no doubt a promising field of investigation. Technical difficulties, however, are met with which can be mastered only by a team of workers trained for this particular purpose.

We want to prove in this paper that, in the meantime, useful conclusions can be drawn from a systematic histological and cytological survey of an extensive series of human thyroids collected in the postmortem room. Such material must be fresh, perfectly fixed and should be collected in an area such as Ghent, Belgium, where endemic goiter is very rare.

Investigations of this kind have been carried out in recent years by Farrant [10] and Williamson and Pearse,[11] but their aim was different from ours. For the present at least we are not concerned with knowing whether, in one particular disease, the gland is hyperplastic or not, or whether the gland has a larger or a smaller hormonic output. We use marked changes brought about by pathological conditions to get new information about the functional interpretation of certain histological structures.

It is well known that infectious or toxic conditions sometimes considerably alter the thyroid morphology. What is more often overlooked is the fact that structures appear which are considered by many as a characteristic feature of toxic goiter. The extensive material at our disposal gives us the opportunity to link up a complete series of transitional changes, the study of which leads

to a satisfactory explanation of the extreme stages. We are thus able to connect the morphology with certain aspects of functional activity.

The Morphology of the Thyroid Epithelium during Follicular Depletion (Colloid Release)

The first point we shall consider is the morphology of the thyroid epithelium during follicular depletion. The work of our predecessors, as well as our own investigations, shows that colloid release is a common occurrence in toxic or infectious processes, but it is by no means constant. In 6 cases of pneumococcus lobar pneumonia we never saw any sign of it. Neither did we notice any depletion in acute streptococcal puerperal septicemia. In acute peritonitis following appendicitis, on the other hand, we found regularly a certain degree of colloid release. In patients dying from intestinal obstruction (11 cases) all the gradations of the process exist, so that finally the follicles are found to be reduced to canalicular formations which resemble in all respects similar structures seen in toxic goiters. The same remark applies to diphtheria cases, although in these there is no general rule, intercurrent infection probably accentuating the depletion.

Figures 1 and 2 represent the thyroid of a female, 54 years old, who died within 48 hours after the onset of intestinal obstruction; Figure 2 particularly shows the early stages of the depletion. Many follicles, however, are still filled to a maximum, as in Figure 1. The morphology of the epithelium offers many striking features. First of all, the epithelial lining is heterogeneous, contrary to what is generally stated in standard textbooks. To our knowledge only Aschoff [12] has laid stress on this fact. A narrow segment of high cylindrical cells with dark hyperchromatic nuclei is very evident, while the remaining epithelium is either low cuboidal or endothelioid. Thus we already can distinguish three types of epithelium in one follicle, low cuboidal (Type 1), columnar (Type 2), endothelioid (Type 4). Let us now examine the follicle on the left of Figure 2 and neglect for a moment the typical "Sanderson Polster." The high cylindrical segment is slightly extended. It is doubtful if in this follicle colloid release has begun. We should like to draw attention to the appearance of another type of cell, especially in the

groove adjacent to the "Polster." It is a high cuboidal cell with a large vesicular nucleus (Type 3). A general survey of 500 human thyroids from normal and pathological cases proves that all the varied aspects of the thyroid epithelium can be classified under these four types.

The follicle on the right of Figure 2 shows an unquestionable depletion. Its shape tends to be more or less triangular, while the high cylindrical epithelium extends over two-thirds of the contour.

In Figure 3 again we notice the close connection between the extension of this type of epithelium and the progressive collapse of the follicle. On the left the shape of the two adjoining follicles A and B proves that they are completely filled with colloid. A high cylindrical segment is easily recognizable in both, but it is narrow. On the right of this figure (follicles C and D) these high cylindrical segments extend over the greater part of the follicular wall, while the colloid depletion is already marked. This is still more convincingly emphasized in Figure 4 from another case of intestinal obstruction. Here the follicle is completely surrounded by high palisade epithelium of which the morphology is clearly demonstrated on higher magnification. We need not dwell upon its histological characteristics, except to point out the fact that the width of the cell does not far exceed the width of the oval, hyperchromatic nucleus.

We suggest that there is a close connection between the increase in the size of the segments of cylindrical epithelium and colloid depletion. Since we believe that this point is of importance in thyroid histology, we should like to present further data in favor of this assumption. Figures 5, 7 and 8 represent thyroids from diphtheria cases. Of the four large follicles present in Figure 5 the third from the left shows a beginning stage of depletion. Here the high cylindrical epithelium forms the least extensive segment. In the second and fourth follicles from the left, collapse of the follicle is much more marked. In the one where it is most evident (the fourth), the greatest part of the lining is columnar. Figures 7 and 8 again show this striking correlation; the generalized high cylindrical character of the follicular epithelium corresponds to extreme degrees of colloid absorption. Stress is laid upon the fact that in the human thyroid a large spherical follicle is never found with an entirely uniform, high columnar lining. When this type of epithelium surrounds the follicle entirely, the latter has always attained an extreme degree of de-

pletion. Of course, we find in our preparations sections of collapsed follicles without columnar epithelium. Serial sections prove, however, that they correspond to the tail end of a diverticulum of a depleted follicle, the main body of which, not seen in this particular section, is provided with large high cylindrical segments. Others are depleted follicles of which the epithelium shows regressive changes; they are devoid of functional activity. We may summarize our conception as follows: in a follicle provided with uniform and generalized high cylindrical epithelium, the colloid resorption is always considerable. As shown above the reverse is not true, *i.e.*, a depleted follicle may be found occasionally without cylindrical lining.

The above observations force upon us the conclusion that the columnar epithelium absorbs the colloid stored in the follicle and excretes the active hormone into the blood or lymph vessels. We see some cytological evidence of this excretion in the form of colorless basal vacuoles found only in this type of epithelium, as one of us [13] has shown in a recent paper. They attain a considerable size in some cases of diphtheria, as shown in Figure 7.

Moreover, there is always a very marked vasodilatation of the sinusoids adjoining this type of epithelium. The lymph vessels are also distended; in cases of acute depletion this may lead to edema of the stroma (Fig. 7). The excretory function of high columnar epithelium is in itself not surprising since toxic goiters are so amply provided with it. A study of the latter would have led to this conclusion were it not for some exceptions which resulted in confusion. In the light of what follows, these discrepancies, and especially the eventual absence of high epithelium in a toxic goiter, can be easily explained.

The Effect of Colloid Depletion

The result of colloid release on the architecture of the follicle is illustrated by Figure 7. The collapse of the wall leads to the formation of diverticulums which later on sever all connection with the main follicle. In this way accessory minute follicles are formed which, in some instances, as in Figure 8, surround the depleted follicle as satellites. These diverticulums of the main follicle have been noticed since Virchow by many authors (Wegelin,[7] Marine,[14] Wilson,[15] Norris,[16] and Rienhoff[17]). Most of these workers never took into account the part the disease played in the extension of these

secondary acini and considered the diverticulums or secondary acini as evidence of proliferation. A recent work of Moritz [18] also favors this view. Figure 7 proves clearly that this is not the case. Glands presenting this morphology have a low weight. There is actually no budding but a formation of diverticulums through mechanical factors. However, the collapse of the follicular wall is not the only responsible factor. A modification of some of the constituents of the excretory segment also plays a rôle. In protracted cases where the thyroid has been stimulated for some time the columnar and rather dark cells gradually increase in size while the nucleus becomes large and vesicular (Type 3). The turgescence of a row of adjoining cells forces them to bulge out. The effect of the two combined factors is illustrated most clearly in Figure 6, where we notice not only depletion of the main follicle but also a bulging out of the newly formed diverticulum.

It is evident that, when this process of diverticulum formation extends along the entire follicular wall, as can be seen in Figures 4 and 8 (severe collapse), the process leads to a fragmentation of the main follicle. The key to the interpretation of senile involution of the thyroid lies in this important observation.

The Morphology of Intrafollicular Colloid Secretion (Storing Process)

The colloid represents a storage product which in adults is the result of a very slow secreting process operating from birth. On the other hand, there is ample evidence that after acute colloid depletion the colloid can be restored quickly to normal.

One of us [13] has carefully followed this slow accumulation of colloid in young children who died accidentally. It is a striking fact that up to the age of 12 years the high cylindrical segments are very scanty, so that the morphology of the thyroid epithelium (at this age) is almost uniform and of the low cuboidal type. As this corresponds to a gradual increase in size of the follicles brought about by a process of coalescence we concluded that low cuboidal epithelium slowly secretes colloid into the follicular cavity.

Figure 9 illustrates the appearance of the epithelium during an active process of intrafollicular secretion. The follicle represented in the center of Figure 9 has reached an extreme degree of depletion.

It belongs to a thyroid from a case of intestinal obstruction where the patient survived 4 days. A very narrow segment of high cylindrical cells is still evident. In our opinion these cells represent remaining segments of the excretory (or absorptive) function. The other cells have undergone marked changes. These cells have broadened out, their nuclei have become vesicular and increased in size and they have the characteristics of cell Type 3. They are secreting into the follicular cavity large droplets (Anderson vacuoles) and at the same time a watery, transparent fluid. We see here a striking example of the beginning of a new and very active colloid secretion. A more advanced stage is seen in Figure 10. It is from the thyroid of a child who had passed the stormy period of diphtheria and was actually convalescent. The child died suddenly of heart failure 18 days after the onset of the disease. Small doses of iodine were administered daily during the illness. The thyroid shows marked changes. The follicles are of medium size (80 to 100 microns in diameter) and much smaller than in children of the same age who die accidentally (100 to 150 microns). Most probably this thyroid underwent, during the acute stage of the disease, a period of depletion comparable to that represented in Figures 7 and 8. However, at the time of death the gland was rapidly restoring its colloid material, since almost all follicles are spherical and filled with a thin, transparent fluid. Moreover, evidence of follicle coalescence, such as Moritz [18] recently described in man and Uhlenhuth [8] in the salamander, is frequent. The newly accumulated colloid stands out in contrast to the older, denser colloid, lying in the center of the follicular acinus. Here again, as in the previous preparation (Fig. 9) the epithelium is composed of large cells with large vesicular nuclei (Type 3). If it were possible to present an unlimited number of photographs, we could easily demonstrate the frequency of similar aspects in subacute septic processes, such as peritonitis following appendicitis (7 to 9 days duration).

These observations lead us to the conclusion that the high cuboidal cells (under certain conditions large cylindrical), which contain a large hyperchromatic nucleus and clear cytoplasm with an extensive surface contact with the blood vessels, secrete the colloid into the follicle actively and rapidly. Experimental data support this view. Injection of pilocarpin into guinea pigs and rats increases the intrafollicular mass of colloid and transforms a low cuboidal

epithelium into a high cuboidal type. We also find the latter form of epithelium in rats which, having been exposed to cold, restore their colloid at room temperature. It is well known from the work of Cramer[19] that exposure to cold causes a severe colloid release and it may be interesting to note incidentally that during the depletion period high cylindrical epithelium occurs, a fact that agrees with our conclusions.

The functional significance of endothelioid epithelium is obvious, namely that of a slow secretion of colloid.

The Morphology of the Normal Thyroid

Keeping in mind the functional significance of these different types of epithelium, a survey of human thyroids of adults who died soon after accidental injuries leads to a new conception of thyroid histophysiology. The epithelium of normal control glands is in fact heterogeneous. Although the predominant type is low cuboidal, narrow segments of high columnar cells are present in some of the large follicles. If our previous observations are correct, the number and size of these columnar cell segments should give us an indication of the hormonal output of the gland. They represent the only part of the parenchyma that sets free the hormone into the circulation.

This active part is very small if we consider the fact that only one of five large follicles shows these narrow excretory segments. This observation is in harmony with the histophysiology of other endocrine glands, such as the suprarenal cortex, where the available evidence points to the fact that likewise only a very small proportion of cells is actively at work under normal conditions, while the remainder of the parenchyma is held in readiness for special emergencies.[20]

We have come to the conclusion that in normal glands the high columnar segments can be divided into two groups. An example of the first group may be seen in Figure 1, where there are no accessory follicles. In most instances, however, we notice that they are in close contact with small secondary satellite follicles generally provided with low cuboidal epithelium and formed by a process described above (second group). These peculiarities are convincingly demonstrated in Figure 11, which shows a thyroid from a man 21 years old who was killed in a motor accident.

The "Sanderson Polsters"

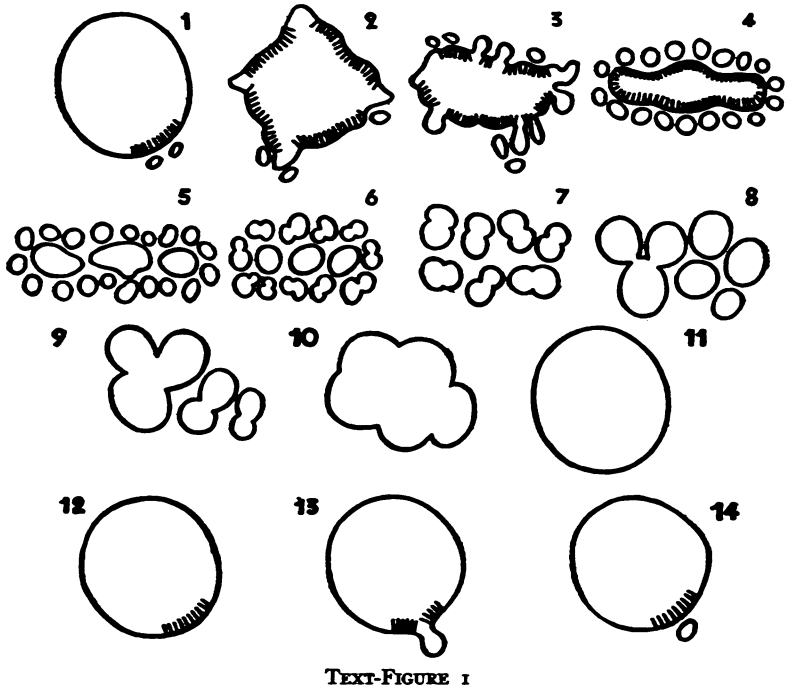
When colloid secretion increases in the small secondary follicles their mass bulges into the follicular cavity and gives rise to a "Sanderson Polster" (Fig. 2) for which we suggest the term "papilla." These secondary acini are nearly always lined with large epithelial cells (Type 3) and the nuclei are conspicuous by their size. These papillae, or "Sanderson Polsters," are a common finding in septic or toxic processes which stimulate the secretion in those secondary acini. Up to the present time the "Sanderson Polster" has been considered a center of proliferation. In our opinion it is the expression of a simultaneous stimulation of hormonal excretion by the columnar epithelium of colloid secretion by the cells with large nuclei, which are restricted to a small portion of the follicle complex. We believe that the papillary formation is due to three factors: increase in size of the cells, increase of colloid secretion and congestion of the capillaries.

These papillae consequently correspond to localized zones of functional activity, normally present, but brought into prominence by the stimulation of physiopathological conditions. In the light of these observations the significance of the small acini is quite different from that of the large follicles. Only the latter excrete the hormone into the circulation. As shown above, the two types are, however, closely related. High columnar cells having performed their excretory function become turgescent and are extruded in the form of acini out of the main follicle, the process being accentuated by the depletion of the latter.

The Functional Unit

We believe, therefore, that the human thyroid is composed of functional units, *i.e.*, complex formations of main and secondary follicles. In many cases of severe sepsis these histological features are evident and no better illustration can be given than by Figure 8. Under normal conditions the functional units are less conspicuous because the colloid storage overshadows the signs of colloid absorption. The greater part of the epithelium continues to increase the storage of colloid slowly, while in some main follicles only a small segment of cells excretes the hormone into the capillaries (Figs. 1 and 11). The concept of the functional units was brought

forward by Williamson and Pearse,[11] but their argument is weakened by the excessive stress they lay upon the significance of the lymphatic system, which in fact does not differ essentially from that of any other endocrine gland. The same concept has been implied by those workers who have made reconstructions of the thyroid follicle since the publication of Wilson.[15] However, the only way to obtain convincing evidence is to make a study of glands profoundly changed by the physiological effect of pathological conditions.



TEXT-FIGURE 1

In health and disease the active functional units are ever-changing structures. With a constant number of cells the functional demands of the gland are met by various appropriate cell combinations.

In the early stages of a septic or toxic process the thyroid unit reacts by a stimulation of both excretion and secretion, which compensate for each other. The segments of high cylindrical cells extend, while the low cuboidal cells of the main follicle change into cells with large nuclei (Type 3), a process which brings the "Sanderson Polster" into prominence. This period of *compensated activity*

lasts a variable time. In 5 cases of streptococcic puerperal infection we found evidence of it from 8 to 10 days after the onset of fever. In peritonitis following appendicitis, in several cases of diphtheria and in protracted cases of staphylococcic pyemia, there is evidence of an early depletion. The *decompensation* is still more pronounced in intestinal obstruction. On the other hand, several cases of peritonitis following appendicitis which we have studied prove that the depletion and fragmentation can be followed by a restoration period leading, through a process of coalescence of the follicles, to the normal configuration of the functional unit (Text-Fig. 1).

The succession of periods of colloid release and colloid secretion appears as a fact of general significance in the histophysiology of the thyroid. Uhlenhuth's [8] remarkable work proves that metamorphosis in *Ambystoma opacum* requires an activity of the thyroid which leads to a considerable colloid depletion. However, a period of active restoration of the colloid soon follows. Kuhn,[21] on the other hand, noticed this same succession of hormonal excretion and intrafollicular colloid secretion in salamander larvae injected with thyrotropic hormone of the anterior lobe of the pituitary gland. In man (Van Goor,[22] Schmelling [23]) and in mammals (Benazzi [24]) colloid release is observed in the later part of fetal life. As Benazzi has shown, the follicles at birth are already refilled when the animal is born active (such as the guinea pig or the lamb). In other mammals, such as the mouse and rat (Benazzi) and man (own observations) the colloid restoration takes place soon after birth.

Discussion

We are well aware that our conclusions may lead to controversy. Any one familiar with the histology of toxic goiter will be prepared to accept the excretory function of the high columnar epithelium (*i.e.*, colloid absorption or release with hormonal output into the circulation). In fact, Holst[25] has already suggested that the absorption process takes place at the site of the "Sanderson Polsters." But this idea was more or less hypothetical. The critical mind will point to toxic goiters devoid of this type of epithelium. If Graves' disease or thyrotoxicosis centers entirely in the thyroid, which is far from being an established fact, our morphological studies suggest that, besides the unquestionable multiplication of its cell constituents, the thyroid shows the decompensated type of hyperfunction when no pre-

operative iodine treatment has been used. The functional units resemble in many respects those of a case of diphtheria, apart from the hyperplastic characteristics (Fig. 8). We have shown that in this type of hyperfunction a phase of colloid restoration very often follows the phase of depletion. In appendicitis there is even evidence that both processes alternate. The discrepancy in the histological findings in goiter material may be easily explained by the fact that the gland is removed during such a period of restoration. This temporary lack of thyroxin excretion need not necessarily correspond to an improvement of the symptoms, since the thyroxin is very slowly destroyed in the tissues.

There are other objections to be met. One could argue that the colloid depletion is not the result of the functional activity of columnar cells but that the morphology of the thyroid epithelium is controlled by the collapse of the follicle. This argument does not hold. In rats exposed to cold the small size of the follicles, or more exactly the difference between their diameter and the height of the cells, is so slight that collapse is not possible and yet high cylindrical cells appear at a given moment during the experiment.

In the literature columnar epithelium has generally been interpreted as a sign of hypertrophy and has been associated with cell proliferation. Marine [14] says that "columnar epithelium always indicates hypertrophy." With this we cannot agree. Columnar epithelium is a normal constituent of the gland. Its scarcity explains why it has been overlooked up to the present. In any human control gland we have had no difficulty in finding columnar epithelium grouped in narrow rows. When in simple colloid goiter these columnar cells become very evident, Wegelin,[7] Aschoff [12] and Hellwig [5] consider it a sign of proliferation. There is no convincing argument in favor of this assertion. In our opinion the increase in number and in size of these columnar segments coincides with the onset of toxic symptoms, and indicates that the hormonal output is increased. This is much more in agreement with clinical observations. It will be interesting to reëxamine simple colloid goiters from the point of view of the existence of columnar segments. If we find them regularly a much debated problem will be solved, we shall understand at last why in spite of their low cells most of these goiters are not accompanied by thyroid insufficiency. Aschoff,[12] who has based his classification partly on the existence of

the so-called proliferating buds provided with columnar epithelium, admits that the presence of the latter coincides with the appearance of symptoms of hyperthyroidism. If we compare these observations with ours, it must be conceded that they lend support to our views.

The chief argument of those who believe that high cylindrical epithelium indicates cell proliferation consists in the fact that adjacent to this type of epithelium there is always an active process of budding. That is why the Sanderson formations have been considered proliferation zones. To this we answer first of all, that in no freshly fixed human gland does one find isolated cells budding from high epithelial cells; they are always grouped in acini with a definite lumen. Secondly, we point again to the mode of formation of these secondary acini where only mechanical factors play a part.

We do not deny the possibility of a multiplication of cells in the papillae, but so far no one has given decisive proof of it. In our fresh human material we have never found mitotic figures. Of course we do not lay stress on this because we are dealing with agonal conditions. However, in thyroids of rats, guinea pigs and rabbits we have repeatedly found mitotic figures in both low and high epithelium with the same frequency. In exophthalmic goiter, where the different types of cells described above are present, mitoses are found in any one of them. What is still more convincing is the fact that the weight of the glands with a preponderance of columnar epithelium (Figs. 7 and 8) is less than the average (5 gm. instead of 7 gm. average weight; 3.5 gm. instead of 5 gm. average weight). We had the opportunity of examining several specimens of thyroids from males and females between 50 and 65 years of age killed accidentally. Extensive segments of columnar epithelium were present, as well as secondary acini. If these formations indicate proliferation why should the gland decrease in weight, as our measurements have shown? In the thyroid of salamanders Uhlenhuth noticed also that mitoses were scanty at a period when papillae with high cells were numerous.[8]

Moreover, recent observations support the view of the excretory function of columnar epithelium. As mentioned before, Van Goor [22] and Schmelling [23] have proved that in the later part of human fetal life the colloid is released to a certain extent. In fresh material we find that during that period, and especially at birth, the epithelium is chiefly columnar. Moreover, in the experiments of Okkels, Krogh

and Lindberg [9] where the hormonal excretion was measured by the basal metabolism, typical columnar epithelium appeared, as is shown in Figure 3 of their publication.

At the onset of metamorphosis of *Ambystoma opacum* the functional activity of the thyroid is unquestionable. Although Uhlenhuth [8] does not distinguish different cell types it is evident from a perusal of his paper that columnar epithelium is present during the colloid release. We should like to call attention especially to Textfigure 16, page 645 of his paper published in *Arch. f. Entwcklngsmechn. d. Organ*, 1927, **109**. The appearance of columnar epithelium during colloid release is also strikingly demonstrated in a series of contributions by Corti's pupils on the thyroids of birds coincident with the development of feathers.[24, 26]

We shall not discuss at length the secretory function of the cells of Type 3 the surface contact of which with the capillaries is always considerable. In fact it is with those cells as well as with the low cuboidal ones that our predecessors have been chiefly concerned. We refer to the classical work of Bensley and the remarkable contributions of Uhlenhuth.[8] We hesitate to dwell on their cytological features for fear of interrupting the unity of our argument. More about this question will be found in a paper by one of us.[13] We believe that Langendorff cells are compressed cells without any functional significance. Furthermore, we shall not take up the question of the inversion of polarity set forth by Cowdry or the significance of the modifications of the colloid and the Anderson intra-acinar vacuoles (Uhlenhuth,[8] Aron [27]) which are no doubt related to an increased activity of the gland. The Anderson vacuoles pass from the cell into the follicular cavity. Our photographs and Uhlenhuth's drawings entirely agree. The Anderson vacuoles constitute one of the aspects of rapid intrafollicular secretion and in Uhlenhuth's observations, as well as in our own, their number attains a maximum when the colloid restoration is well on the way.

It will be noticed that we have not mentioned the Wölffler cells or solid interstitial cell groups. Nothing in our extensive investigations supports their embryonic nature. In normal childhood there are no isolated interstitial cells or cell groups. They appear only when the functional units have been stimulated (see also Aschoff,[12] and Rienhoff [17]) and broken up into small follicles through protracted toxic or septic conditions, or through senile involution.

They are formed only when small or medium sized follicles are predominant.

We have come to the conclusion that the parafollicular cells (Nonidez [28]) of small mammals are homologous to the small satellite follicles of the human thyroid. Mechanical conditions (small size of the follicle) prevent the collapse and folding of the follicle wall and only the second mechanical factor mentioned previously plays a part, namely the turgescence of the cell. The process has been clearly described by Florentin [29] and Nonidez.[28]

Bernard,[30] Benazzi [24] and Florentin [29] have suggested that these cells or cell groups excrete the hormone actively into the blood stream. Examination of material from small mammals may favor this view, as does also the cytological structure of these cells and their close connection with the blood vessels. However, a wide experience with the human thyroid compels us to discard entirely this opinion. Furthermore, the predominant histological features of toxic goiter are completely opposed to this theory.

Conclusions

1. Four types of epithelium exist in the normal human thyroid: (1) the low cuboidal type which secretes colloid slowly into the follicular cavity; (2) the large high cuboidal or broad cylindrical cell type with large nuclei which secretes colloid actively into the follicular cavity; (3) the columnar type which absorbs the stored colloid and excretes the hormone into the blood or lymph circulation; and finally (4) the endothelioid type which is associated with a very slow colloid secretion.

2. The thyroid cells are grouped in ever changing functional units which under normal conditions differ from each other by their hormonal output.

3. The units containing narrow columnar cell segments (a normal constituent of the gland) excrete the hormone actively into the circulation.

4. These active functional units are composed of a main follicle and satellite follicles. The excreting zone of columnar cells is always located in the main follicle and usually in close connection with satellite follicles. The remaining epithelium of the functional unit is for the most part low cuboidal and under certain conditions

endothelioid. Occasionally some cells with large nuclei are present in the satellite follicles.

5. Under normal conditions the amount of stored colloid is kept fairly constant by the compensatory activity of columnar epithelium on the one hand and cuboidal epithelium on the other.

6. The small satellite follicles are derived from the excretory segment, not as the result of a budding process but through the action of two mechanical factors: (1) the folding of the excretory epithelium following depletion, and (2) the turgescence of the columnar cells that have exhausted their excretory function. The latter factor may operate alone. The small satellite or secondary follicles represent cell groups beginning anew their functional cycle.

7. There are no interstitial cells or solid interstitial cell groups present in the normal infant or adult thyroid, while in senile involution they may become apparent. This observation refutes the embryonic nature of these elements.

8. "Sanderson Polsters" are the result of functional stimulation of the excretory zone which expands, and of the group of underlying acini which secrete colloid more actively. This papillary formation is caused by an increase in size of the cells, an increase of the colloid secretion and vasodilatation.

9. Although we do not deny the possibility of cell multiplication in high columnar segments or in the "Sanderson Polsters" we maintain that they are not specifically proliferation centers under normal conditions.

10. A very small proportion of thyroid cells excretes hormone into the circulation.

11. Under pathological conditions the gland reacts at the beginning by an extension of the columnar excretory segments and by the transformation of the low cuboidal type into the cell type with large nuclei. At this stage there is no depletion. Increased hormonal excretion into the circulation is compensated for by increased intrafollicular secretion. This compensated stage may last 10 days (streptococcic septicemia). In cases of peritonitis following appendicitis, intestinal obstruction, and occasionally in diphtheria, there is evidence of an early decompensation, the excretion predominating over the intrafollicular secretion.

12. The depletion of the main follicle leads to the formation of secondary acini and finally to extensive fragmentation of the func-

tional unit. The latter may be restored to its normal features through the secretory activity of the small follicles which fuse together. There is evidence of alternating periods of colloid release and colloid storage during protracted infectious or septic diseases.

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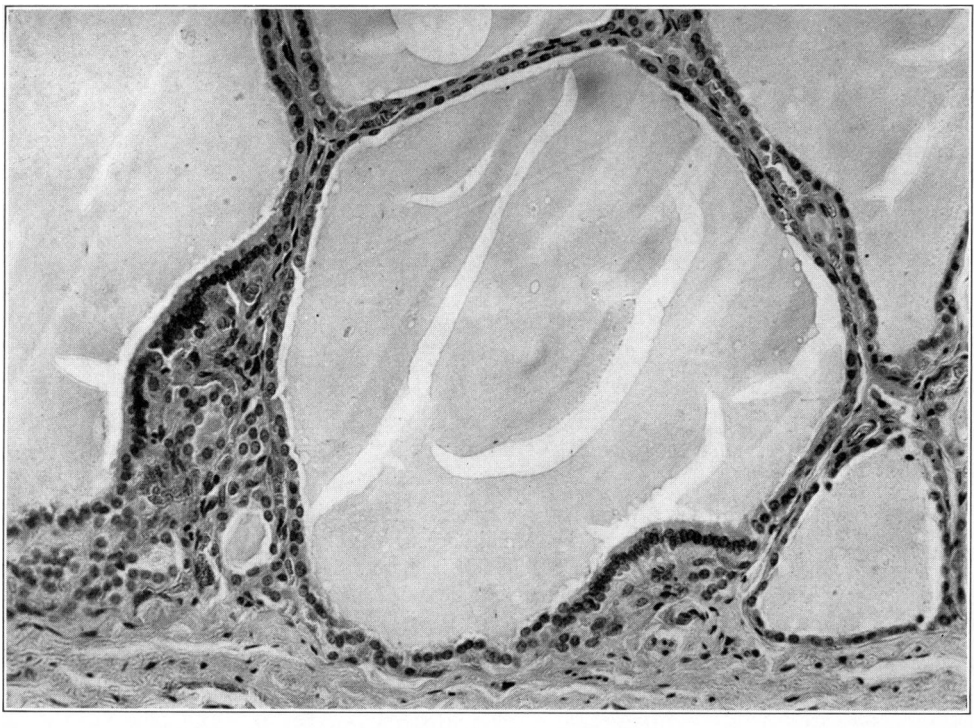
DESCRIPTION OF PLATES

We are indebted to Mr. F. Pittock for the photomicrographs. These were made through the kindness of Professor J. P. Hill, of the Department of Histology, University College, London.

PLATE 153

FIG. 1. Thyroid from a woman 54 years old. Intestinal obstruction by strangulated umbilical hernia. Survival 2 days. Distended follicle. Heterogeneous epithelial lining. Narrow columnar segment slightly protruding into the follicular cavity. Turgescence of the nuclei of the underlying sinusoids. × 300.

FIG. 2. Follicle from the same case showing slight colloid release. Four types of epithelium — endothelioid, low cuboidal, cells with large nuclei and columnar. The columnar is larger than in Fig. 1. Vasodilatation of the underlying capillaries, satellite follicles. "Sanderson Polster" protruding into the follicular cavity. × 300.



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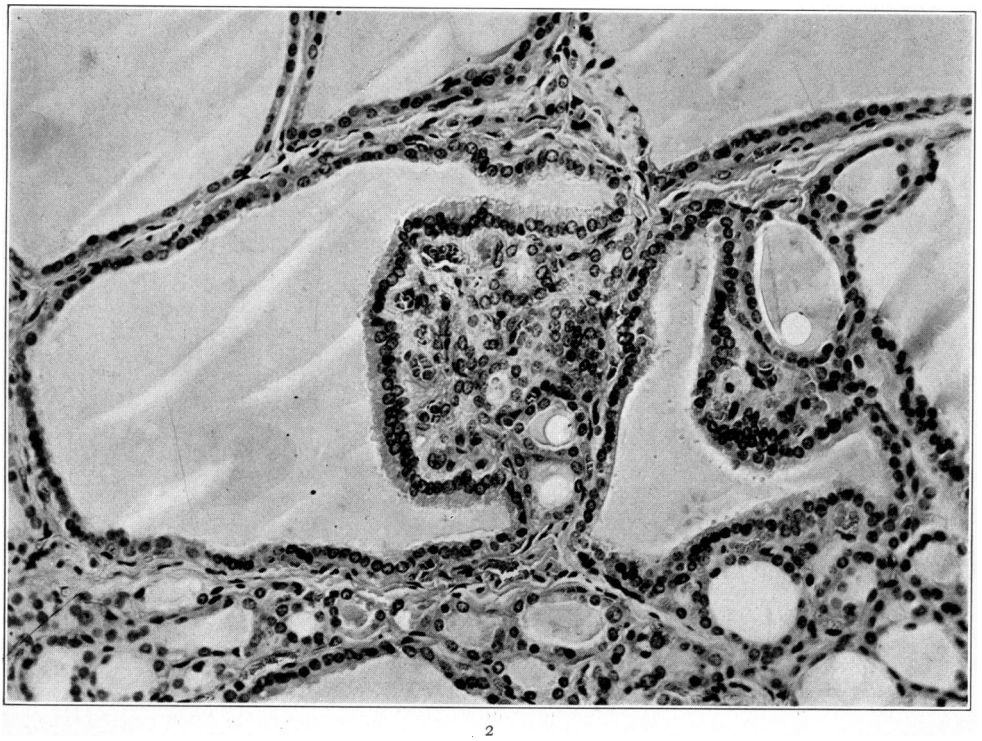

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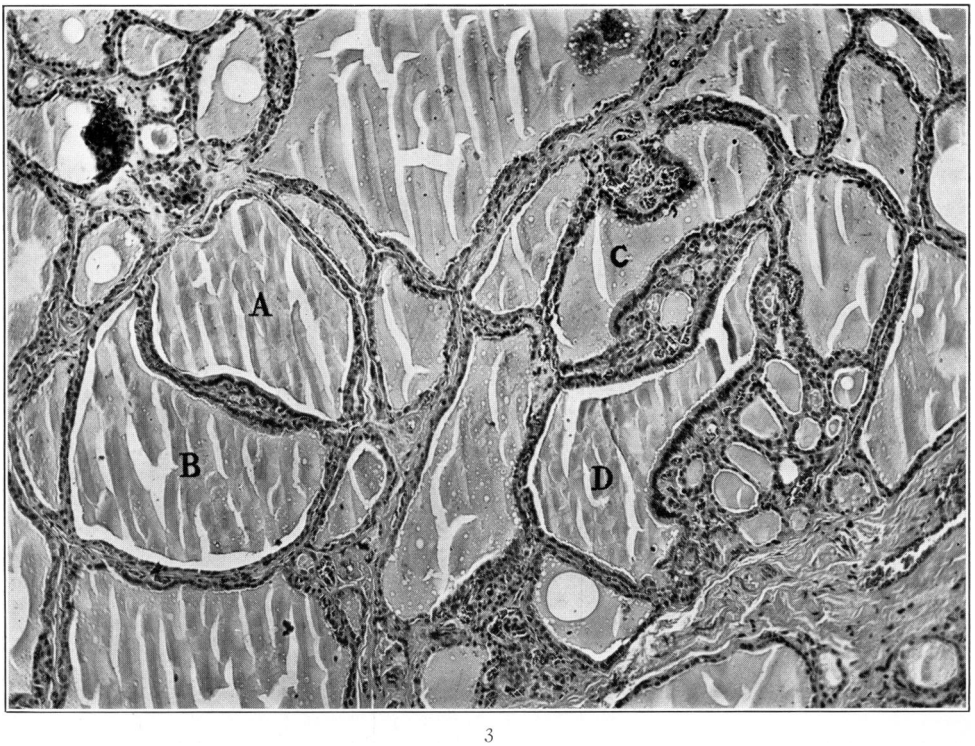
PLATE 154

FIG. 3. Thyroid from the same case at lower magnification showing the correlation between the extension of columnar epithelium and colloid depletion. × 150.

FIG. 4. Thyroid from a woman 70 years old. Intestinal obstruction caused by a scirrhous carcinoma of the sigmoid colon. Survival 10 days. Advanced stage of colloid depletion. The follicle is surrounded by uniform columnar epithelium. Note apical colloid granules. Marked formation of diverticulums and satellite follicles provided with a lining of cells with large nuclei (Type 3). × 500.



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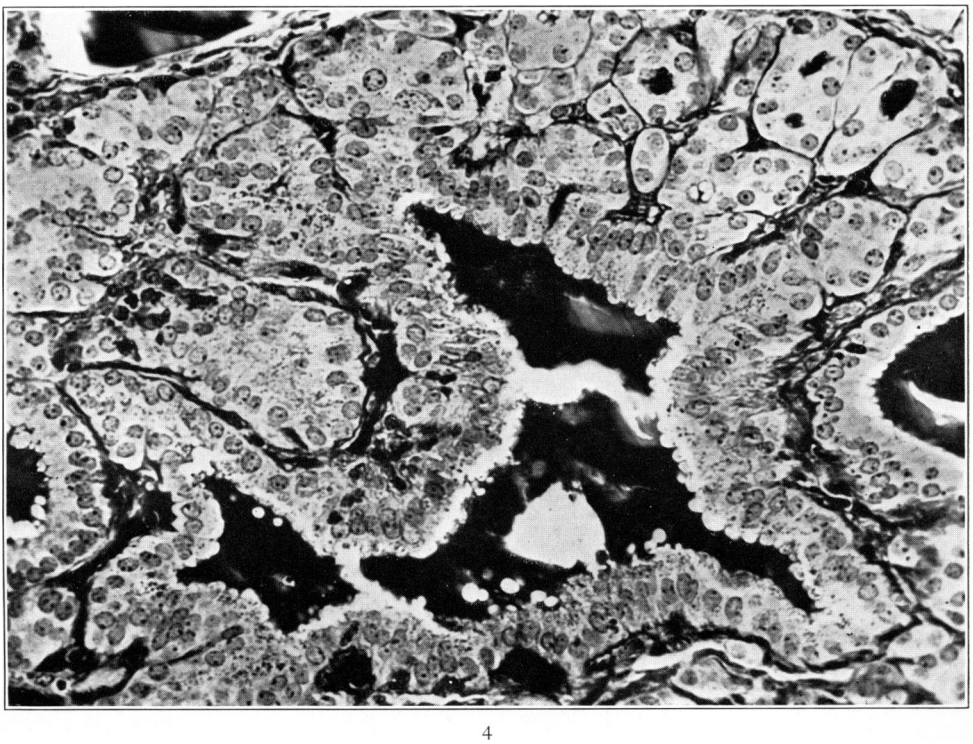

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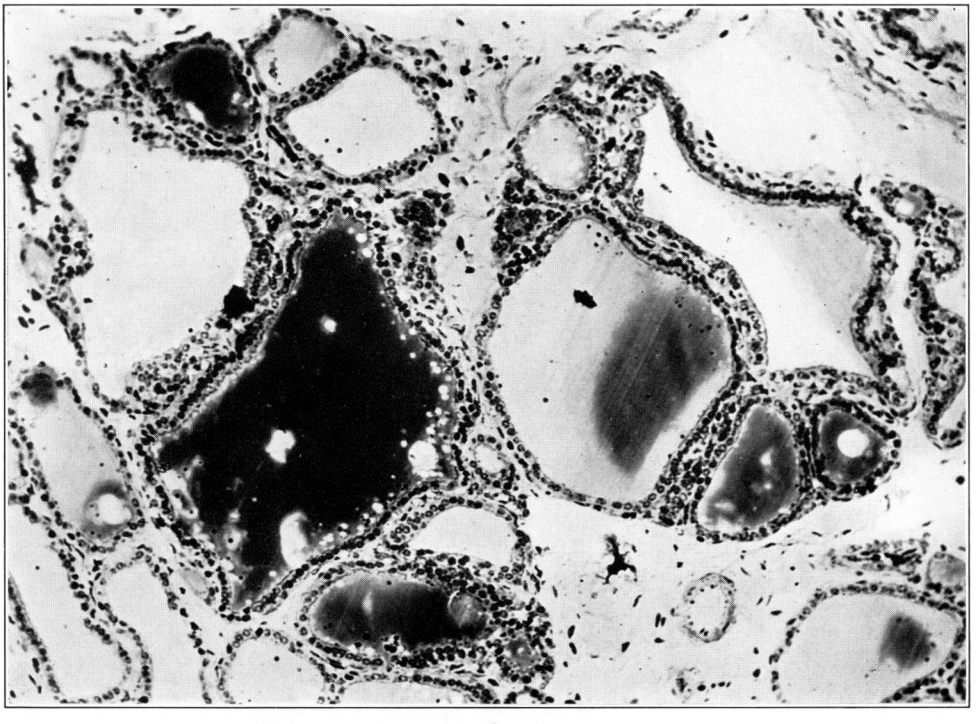
PLATE 155

FIG. 5. Thyroid from a girl 7 years old. Diphtheria, toxic symptoms. glomerulonephritis. Region of the thyroid showing the correlation between the extension of columnar epithelium and colloid depletion. × 230.

FIG. 6. Thyroid from a woman 54 years old. Intestinal obstruction. Morphological features of diverticulum formation (cells with large nuclei). × 230.

FIG. 7. Thyroid from a girl 7 years old. Diphtheria. Acute clinical course. Severe depletion of a follicle. Diverticulum formation. Note the clear zone at the bottom of each cell. Edema of the stroma. × 300.



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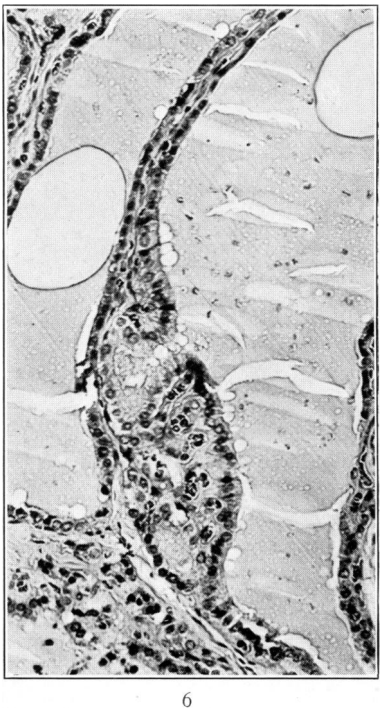

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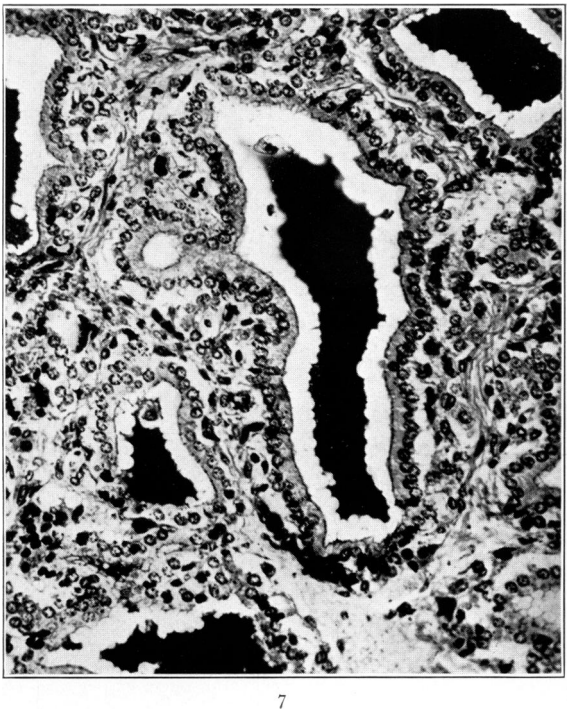

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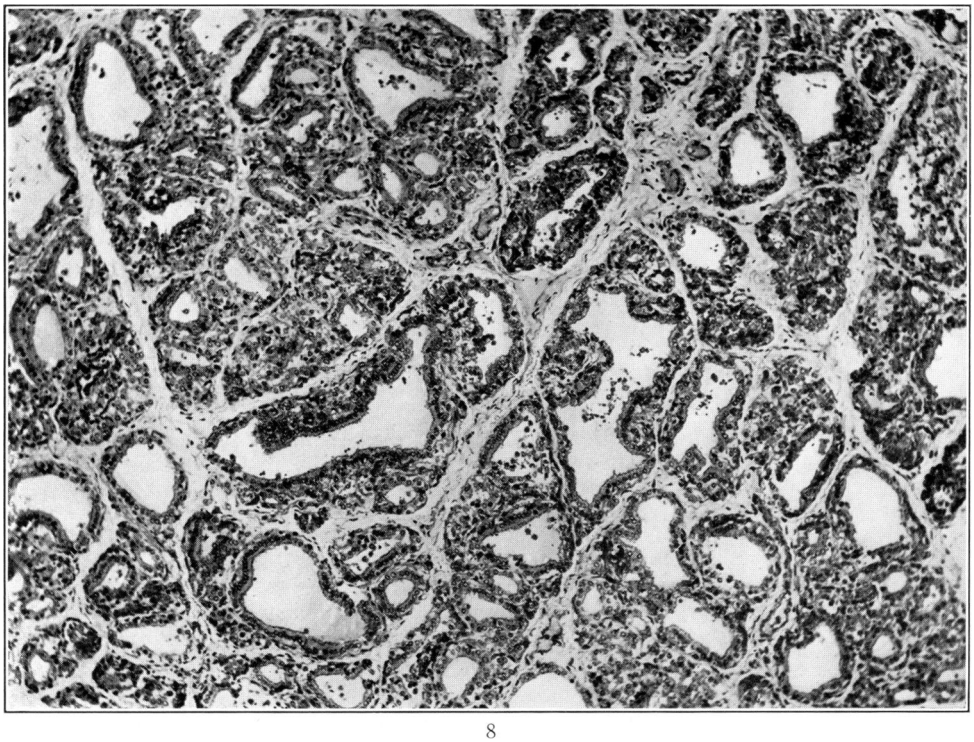
PLATE 156

FIG. 8. Thyroid from a girl 5 years old. Acute diphtheria. Severe colloid depletion. Extensive development of columnar epithelium. Marked formation of satellite follicles. Functional units very evident. × 150.

FIG. 9. Thyroid from a woman 57 years old. Intestinal obstruction by strangulated umbilical hernia. Survival 4 days. In the center of the photomicrograph is a collapsed follicle filled with a clear colloid. Note a narrow columnar segment. The remainder of the epithelial lining is composed of cells with large nuclei. Secretion of apical vacuoles (neosecretion). × 500.



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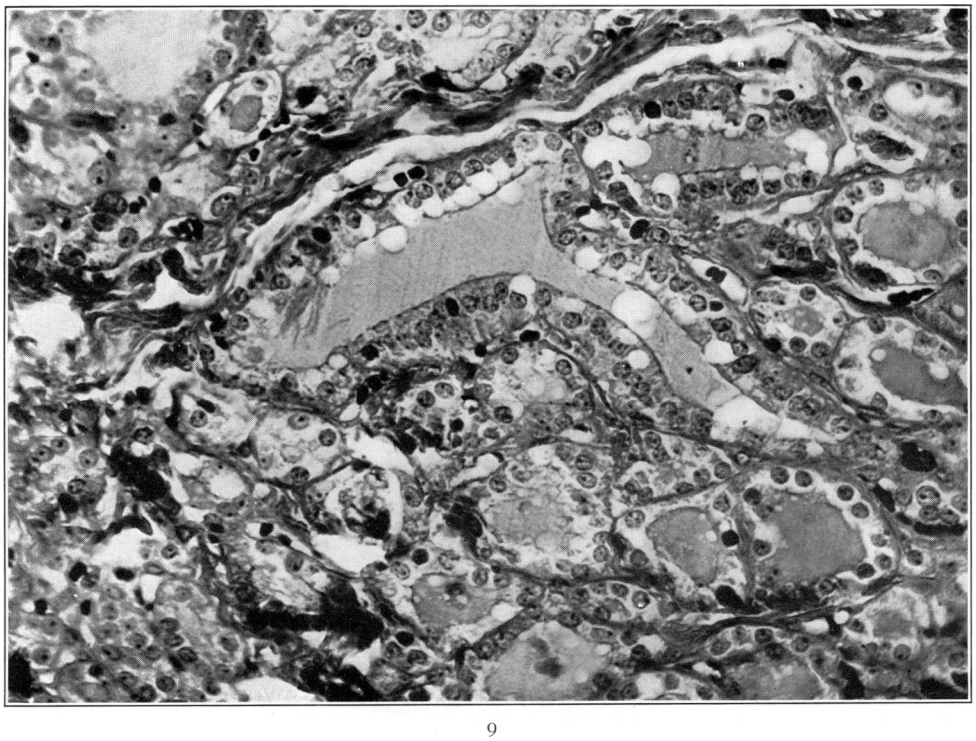

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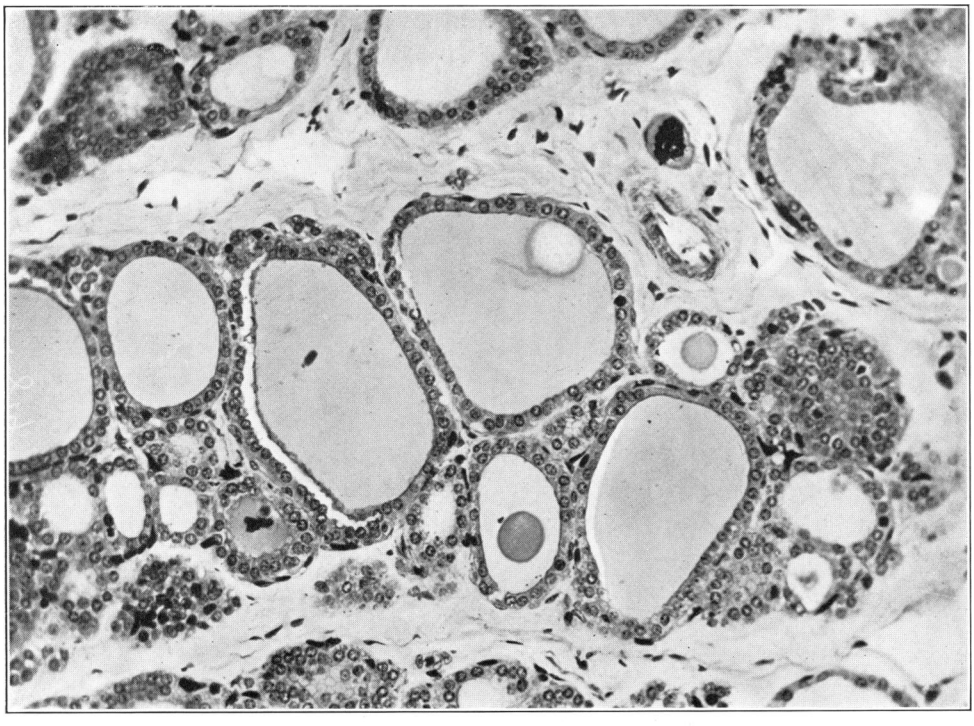
PLATE 157

FIG. 10. Thyroid from a girl 9 years old who died suddenly during recovery from diphtheria. Stage of restoration of the colloid. The old, denser colloid can be seen in several follicles. Uniform aspect of the epithelial lining of the distended follicles (cells with large nuclei — Type 3). × 300.

FIG. 11. Thyroid from man 21 years old. Fracture of the skull. Survival 48 hours. Specimen not fresh. Note the three excretory segments (columnar epithelium) belonging to three adjoining functional units, and the group of satellite follicles which lies under each columnar segment. × 230.



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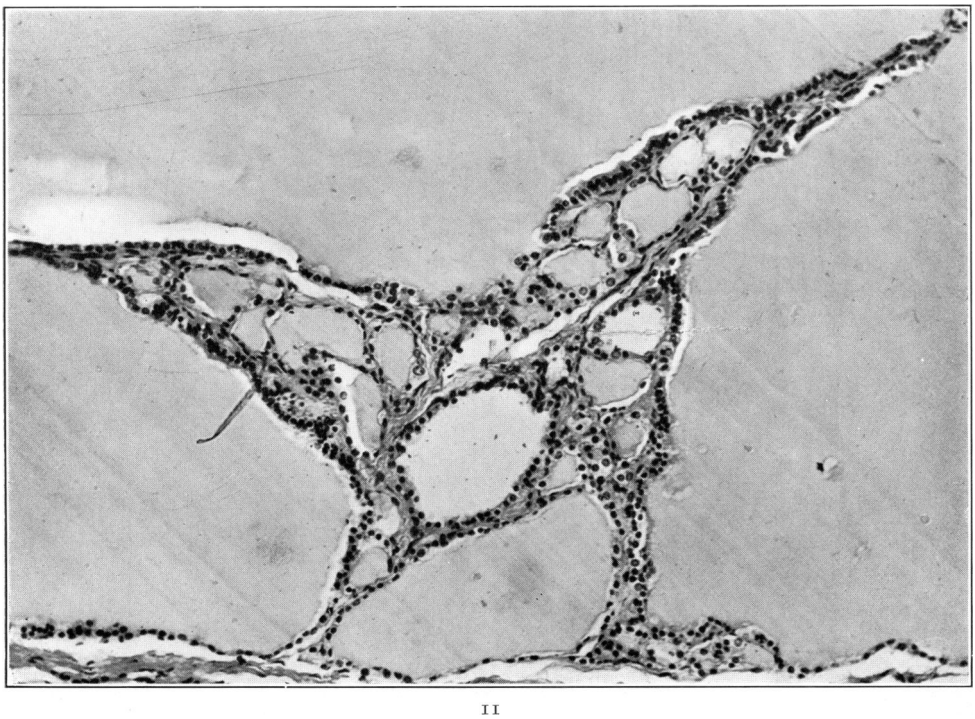

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